A. Address Ethical Concerns

Comments on ethical concerns revolve around three topics; (1) whether humans present in the EUP testing area should be considered human subjects and the testing be subject to the requirements of human studies rules; (2) OX5034 might be useful to communities with a limited tax base and thus be an environmental justice consideration; and (3) sacredness of the natural world and its preservation.

1. Human Subjects and Informed Consent

Forty-four comments questioning whether humans in the test area should be considered research subject were received. (0014, 0031, 0038, 0058, 0088, 0092, 0096, 0097, 0101, 0106, 0113, 0118, 0119, 0128, 0129, 0134, 0135, 0136, 0148, 0171, 0184, 0189, 0193, 0204, 0206, 0213, 0214, 0228, 0237, 0245, 0275, 0284, 0285, 0287, 0296, 0306, 0317, 0318, 0323, 0329, 0334, 0335, 0342, 0344) Most of these comments simply objected to the testing on the basis of fears of being exposed to OX5034 mosquitoes. These commenters simply indicated that they do not consent to being part of any testing, or stated their belief that informed consent is required for the proposed testing, or voiced concerns that they would be subjects in experiments that they do not support. These commenters do not provide any detailed rationale for the commenters' position. Other comments are more specific. These comments argued that informed consent has to be part of any testing of OX5034 because: (1) OX5034 mosquitoes might interact with humans in the test area; (2) limitations on the use of other methods of mosquito control might affect humans in the test area; and (3) long-term effects of potential interactions between OX5034 and humans have not been studied. Examples of the types of comments received are provided below.

GeneWatch UK (0335) and Center for Food Safety (0344) stated that:

> "We note that, were an experimental use licence to be granted, the requirements of EPA's human studies rule (40 CFR Part 26) should be followed, due to the exposure of human subjects (including children) to the proposed open releases of GE mosquitoes, and the potential limitations on the use of other methods of mosquito control that may need to be applied during the experiments." (GeneWatch UK 0335 p. 13; Center for Food Safety 0344 p. 16)

Commenter D. Rubin (0317) stated that:

> "This is a biological experiment. The mosquitoes will interact with humans in our environment and no one knows all of the implications of that interaction." (D. Rubin 0317 p.1)

Friends of the Earth (0342) stated that:

> "The release of GE mosquitoes as an attempt to curb the spread of disease should be considered a medical trial and must follow the laws and guidelines in place to protect human subjects in medical trials. Central to ethics on human subject trials is the idea of free and informed consent. . . . It is critical that communities, and in particular, the communities that would be on the front line of this experiment, give consent to being part of this experiment. . . Community members must be informed throughout the process through a number of mechanisms, including the establishment of local institutional review boards and ethics committees and hosting of community meetings and public forums. Community members must know the parameters of the trial areas, have a right to leave the field trial areas[1] or demand the halt of the experiment entirely if they so decide." (Friends of the Earth 0342 p. 6)

Commenter M. Daly (0300) contended that in the absence of an Informed Consent process Oxitec had "not obtained informed consent to Legally run this trial." She stated that:

> "Informed Consent is a voluntary agreement to participate in research. It is not merely a form that is signed but is a process, in which the subject has an understanding of the research and its risks. Informed consent is essential before enrolling a participant and ongoing once enrolled. Final Rule revisions of the Common Rule (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/finalized-revisions-common-rule/index.html)." (M. Daly 0300 p. 1)

Commenter M. Daly (0300) pointed out that the Common Rule defines a human research subject as:

> " . . . , an individual whose interests may be compromised as a result of interventions in a research study." (M. Daly 0300 p. 1)

Commenter M. Daly (0300) went on to explain that "interventions" refers to:

> " . . . both to the experimental procedure being investigated as well as to non-experimental data collection procedures. More specifically, a human research subject is an individual: 1) who is directly intervened upon by an investigator as either (a) a recipient of a study intervention or (b) as someone who undergoes non-experimental interventions to collect data; 2) who is deliberately intervened upon via manipulation of the individuals environment by the investigator in such a way as to have a direct effect on the individual; 3) who communicates or has interpersonal contact with an

[1] Macer, Darryl. "Ethical, Legal and Social Issues of Genetically Modifying Insect Vectors for Public Health." Insect Biochemistry and Molecular Biology 35.7 (2005): 649-60.

> investigator for the purpose of collecting data through, for example, interviews, focus groups, or questionnaires; and 4) about whom an investigator obtains identifiable private information for the purpose of collecting data. . . ." (M. Daly 0300 p. 1)

Commenter M. Daly (0300) contended that people in the test area were human research subjects:

> "When their home or property is accessed and the location recorded as a spatial variable for the release or collection of mosquitoes because the precise location of the household is important for entomological reasons and these data constitute identifiable private information at the household." (M. Daly 0300 p. 1)

Commenter M. Daly (0300) went on to state that:

> "I am writing this today to let you know that the process of Informed Consent, which is required by law, was not taken into consideration. Oxitec has never released any safety data in regards to human health during a trial. Based upon their theories they claim it is not necessary." (M. Daly 0300 p. 1)

Commenter M. Daly (0300) added that while a referendum was held in Key Haven on the acceptability of Oxitec testing in the area:

> "There is a distinct difference between a generic vote of uninformed citizens and informed consent." (M. Daly 0300 p. 1)

With regard to the referendum, M. Daly (0300) stated the belief that:

> "A small group of residents believed that the people of the original trial area in Key Haven were properly informed of both sides of this issue and requested that a referendum be added to our local elections and leave it to the people to decide. The FKMCD decided at the last minute to add a Keys wide referendum to the ballot also. The residents of the rest of the Keys were not informed about much other than the Oxitec radio ads running all day leading up to the vote. Key Haven voted against it. The uninformed Keys wide voters passed it by a slight margin." (M. Daly 0300 p. 1)

Anonymous (0237), stating opposition to the testing, indicated that the belief that the federal government did not have the:

> " . . . right to use the residents of Florida and Texas as guinea pigs for an untested hypotheses which might have unknown health ramifications in the future. The majority of these residents aren't even aware of this proposed plan and accepting public comments isn't the equivalent of earning the informed consent of the people." (Anonymous 0237 p. 1)

Commenter C. Tong (0106) stated that:

> "Florida citizens are not guinea pigs for this companies services. Letting rogue genetics into our mosquito populations demands more time for education and Voting." (C. Tong 0106 p. 1)

Anonymous (0148) stated that:

> "OXITEC has admitted that an unknown number of biting females will be released, but no one has conducted clinical tests on consenting, informed, adult humans bitten by these females." (Anonymous 0148 p. 1)[Emphasis in the original]

Anonymous (0148) added that:

> "Experiments with genetically modified organisms should only be conducted in a controlled environment with consenting informed adults, and should never be allowed into the public domain before these clinical and biological tests are conducted." (Anonymous 0148 p. 1)

Anonymous (0204) stated that:

> "Releasing Oxitecs genetically modified mosquitoes goes directly against the Nuremberg Code. Oxitec does NOT have permission to experiment on me." (Anonymous 0204 p. 1)

Along the same lines, Anonymous (0296) stated that because the long-term effects have not been studied:

> " . . . , the release of GM mosquitoes without the informed consent of every individual affected constitutes a human rights violation. This would leave the city or county releasing GM mosquitoes liable. According to the Nuremberg Code: The voluntary consent of the human subject is absolutely essential." (Anonymous 0296 p. 1)

Anonymous (0287) stated that:

> THIS IS DANGEROUS THE PUBLIC AND IS A VIOLATION OF THE NUREMBERG CODE. ....which states: The voluntary consent of the human subject is absolutely essential. .....Without informed consent of EVERY individual who could be affected YOUR LOOKING AT HUMAN RIGHTS VIOLATION." (Anonymous 0287 p. 1)[Emphasis in the original]

Commenter D. Rubin (0317) stated that:

> "As a resident of Florida who will be affected by this experiment and does not consent to being a part of it, I urge the EPA to reject the application of Oxitec, Ltd. who request an experimental use permit (EUP) for the OX5034 Aedes aegypti mosquitoes expressing tetracycline Trans-Activator Variant (tTAV-OX5034) protein (identified by number 93167-EUP-E). I repeat, I do not consent to being a part of this experiment and if you allow the release of the gmo mosquitoes, I will be forced against my will to be part of a human experiment along with all of the children who, if we were war criminals, would be protected from such experimentation under the Geneva Convention, Rule 92. Mutilation and Medical, Scientific or Biological Experiments. (D. Rubin 0317 p.1)

Commenter D. Rubin (0317) stated that:

> They may also modify our environment in a ways we can not possibly foresee, causing far more harm than good. These open-ended experiments in our environment are foolish to say the least, criminal to say the most. What gives EPA or Oxitec the right to tinker with our state--and planet--when EPA can give no guarantee of safety. Can EPA give a guarantee to the people of Florida?" (D. Rubin 0317 p.1)

Commenter J. Birk (0097) stated that:

> "It is illegal to experiment on humans in United States, without their signed consent. These GMO mosquitoes are nothing more than that, an experiment. No one really knows what the long term consequences to the population, livestock, and nature will be." (J. Birk 0097 p.1)

Anonymous 0184 stated that:

> "If this so-called "test" goes unexpectedly, there is no sure way to undo the damage done. Scientists cannot really know how this will negatively effect other plants, animals, and possibly humans. There is no way to opt out of a test that involves the environment around us on such a scale, so such a test is, in-fact, immoral. The Nuremberg Code states that people must have informed consent when it comes to experimentation, as

> well as the ability to opt out. Performing these tests give neither to the people in the areas that will or may become effected by this experiment." (Anonymous 0184 p. 1)

2. Environmental Justice

One commenter, J. M. Conlon, American Mosquito Control Association, (0263), suggested OX5034 might be useful to communities with a limited tax base and thus be an environmental justice consideration. He stated that:

> "OX5034 *Aedes aegypti* mosquitoes are particularly well-suited to suppress vector mosquito populations below disease transmission threshold in smaller, rural communities not possessing the tax base to establish and maintain fully resourced county/municipal mosquito control programs. This is an issue of environmental justice that could be addressed, in large part, by the utilization of OX5034 mosquitoes as control measures." (J. M. Conlon, American Mosquito Control Association, 0263 p. 2)

3. Preservation of the Natural World

Some commenters raised issues revolving around preservation of the natural world. These included; (1) ethical concerns about implementing any strategy that might result in the elimination of a species; (2) the appropriateness at this time of attempting to reduce any insect population in light of the documented decline in insect populations world-wide; and (3) opposition to genetic engineering on the belief that a genetically engineered organism is unnatural. (0008, 0009, 0015, 0039, 0051, 0061, 0069, 0070, 0077, 0099, 0105, 0115, 0118, 0126, 0142, 0157, 0158, 0195, 0197, 0181, 0187, 0316) Examples of these types of comments are listed below.

Anonymous (0008) argued that:

> "My foremost concern is the unforeseen repercussions of trying to eradicate a species, especially in this age of many unintended extinctions. Using the natural world as a testing ground for such gene alteration of a particular species is unconscionable and unethical." (Anonymous 0008 p. 1)

Anonymous (0009) stated that:

> "This method of making the mosquito population sterile and unable to reproduce may be a bad idea in light of the recent research indicating there has been a decline in overall insect populations all over the world. Research conducted in Germany's nature reserves have found that they have a 76% reduction in insect populations in the last 3

> years. I don't think we should be devising plans to further reduce insect populations at this time." (Anonymous 0009 p.1)

Anonymous (0181) stated that:

> "Don't mess with genetics through GMO anything. Messing with genetics is messing with Gods laws and their sacredness which should be preserved and not GMOed." (Anonymous 0181 p. 1)

Anonymous (0069) stated that:

> "Please do the right thing this time and don't allow genetically modified mosquitoes or anything to be continued. Genetically modified food, insects or anything is unnatural and anything unnatural will eventually cause problems for everyone on this planet and already has! This is common sense." (Anonymous 0069 p. 1)

Commenter S.L. Smith (0099) stated that:

> "None of those working on this project is GOD ALMIGHTY, or has His skill in creating creatures; indeed, they're playing in the Devil's workshop and the results thereof can only be harmful! It's not for us to play with the DNA coding of anyone or anything. You've been covering up and lying about the damage done by GMO foods for over a decade now, . . ." (S.L. Smith 0099 p. 1) [Emphasis in the original]

Commenter K. Bell (0126) requested "please leave Mother Nature alone" adding that:

> "As someone whose life has been adversely affected by Lyme Disease this is beyond terrifying! Do you all know that mosquitos suck your blood and can and do infect people with Lyme? Is this population control?" (K. Bell 0126 p. 1)

Anonymous (0187) stated that:

> "Finally, when we alter the environment and ecosystem with manmade organisms, we inevitably alter the susceptibility of the environment." (Anonymous 0187 p. 1)

EPA Response to Part VI.K "Ethical Concerns":

Response to Section VI.K.1. "Human Subjects and Informed Consent." With regard to comments suggesting that humans present in the EUP testing area should be considered human subjects and the testing be subject to the requirements of human studies rules, EPA does not find that the research involved with Oxitec's release of male OX5034 mosquitoes meets the regulatory definition of research involving human subjects. Because the research does not meet the regulatory definition of humans subject and thus does not involve human subjects, it is not

necessary to evaluate whether the research constitutes intentional exposure of human subjects.

With regard to the comment (0300) referencing the Common Rule (40 CFR 26, subpart A) to support the assertion that informed consent of those living in the area of the Oxitec release must be obtained prior to initiating the research, because Oxitec is not a federal agency or conducting research sponsored or funded by a federal agency, the Common Rule does not apply. Rather, because this a private study conducted with the intention of submitting the results to EPA in support of a pesticide registration decision, the relevant standards are found in EPA's Rule for the Protection of Human Subjects of Research (40 CFR 26, Subparts K-L). Under 40 CFR §26.1102(i), "research involving intentional exposure of a human subject means a study of a substance in which the exposure to the substance experienced by a human subject participating in the study would not have occurred but for the human subject's participation in the study." There are three elements to this definition that all must be satisfied for the research to be subject to the requirements of 40 CFR 26, Subparts K-L:

1. Research. According to the rule, "*Research* means a systematic investigation, including research, development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this subpart, whether or not they are considered research for other purposes. For example, some demonstration and service programs may include research activities."
2. Human subjects. "Human subject" is defined as "a living individual about whom an investigator (whether professional or student) conducting research obtains:
   (1) Data through intervention or interaction with the individual, or

   (2) Identifiable private information.

   (3) "Intervention" includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. "Private information" includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) for obtaining the information to constitute research involving human subjects."
3. Intentional exposure. If it was research involving human subjects, did the research involve study of a substance in which the exposure to the substance

> experienced by a human subject participating in the study would not have occurred but for the human subject's participation in the study?

The release of Oxitec mosquitoes under the EUP meets the definition of research. The company is releasing the mosquitoes to gather information in a systematic manner to contribute to the generalizable knowledge on the impact of releasing genetically modified mosquitoes on the local mosquito population.

Moving to the second element of the definition of "research involving intentional exposure of human subjects", the research does not involve "human subjects" as defined by the regulation. The release of Oxitec mosquitoes does not gather any information about living individuals. As the focus of the release, Oxitec would collect information on how efficacious releases of male OX5034 mosquito are at suppressing wild Aedes aegyptii mosquito populations in the test area. None of this information involves data about a living individual gathered through interaction with the individual, or collecting identifiable private information about those who may be present in the area of the Oxitec release. Contrary to comment received (0300), the precise location of households in the testing area does not constitute identifiable private information. Therefore, the research involved with Oxitec's release of mosquitoes does not meet the regulatory definition of research involving human subjects. Because the research does not involve human subjects, it is not necessary to evaluate whether the research constituted intentional exposure of human subjects.

The research does not meet the definition of "research involving intentional exposure of a human subject"; therefore, it is not subject to the requirements of 40 CFR 26, Subparts K-L. This means that Oxitec is not obligated to obtain informed consent of those living in the areas where the Oxitec mosquitoes would be released under the EUP.

EPA Response to Section VI.K.2. Environmental Justice. With regard to the comment that OX5034 might be useful to communities with a limited tax base and thus could be considered to be an environmental justice consideration, the commenter supplied no information supporting this supposition. For this EUP application, the Agency takes no position with regard to the possibility that OX5034, if successful in suppressing wild Aedes aegypti populations, could play a role in environmental justice considerations.

EPA Response to Section VI.K.3. Preservation of the Natural World. With regard to the comment about the ethics of implementing a strategy that might result in the elimination of a species, EPA would note that OX5034 is intended only to suppress native wild Aedes aegypti

populations; populations of wild Aedes aegypti are expected to rebound once releases of male OX5034 Aedes aegypti mosquitoes cease.

With regard to the comment on the appropriateness at this time of allowing any action intended to reduce an insect population in light of the documented decline in insect populations world-wide, EPA is aware of studies documenting the general decline of insect populations world-wide and is studying the issue. The limited testing being proposed under the EUP would not contribute to the general decline of insect populations for several reasons. First, the EUP is limited to a small number of acres (44 acres). Second, OX5034 mosquito is highly targeted to affect only Aedes aegypti insect populations, and thus impacts on other insect species are unlikely.

With regard to the comment on Lyme disease, Lyme disease is an infection caused by several strains of the bacterium Borrelia burgdorferi. The bacteria are transmitted to humans through the bite of a tick infected by the bacterium. In North America B. burgdorferi is spread to humans by Ixodes scapularis (blacklegged tick or deer tick). Although mosquitoes have been reported to carry Borrelia[2], there is no credible evidence that they can spread the disease through their bite to humans.

With regard to the other comments in this category, opposition to genetic engineering grounded in the belief that a genetically engineered organism is unnatural, commenters offered no rationales supporting these comments and these comments are beyond the scope of the NOR.

[2] Melaun C., Zotzman S., Santaella VG., Werblow A., Zumkowski-Xylander H., Kraiczy C. and S. Klimpel. 2016. Occurrence of Borrelia burgdorferi s.l. in different genera of mosquitoes (Culicidae) in Central Europe. Ticks Tick Borne Dis. 7(2)256-263.